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Review

New specific and sensitive biomonitoring methods for chemicals of emerging health relevance

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ABSTRACT

In this publication the challenges to cope for the aim to obtain innovative biomonitoring methods in our laboratory are visualized for di(2-propylheptyl)phthalate, 2-mercaptobenzothiazole, 3,5-di-*tert*-butyl-4-hydroxytoluene, 4-nonylphenol, 4-*tert*-octylphenol, 3-(4-methylbenzylidene)camphor, 4,4′-methylene diphenyl diisocyanate, and Hexabromocyclododecane. For these substances new specific markers were explored based on animal or human kinetic data with urine being the preferred matrix compared to blood. The determination of these markers was complex in all cases, because the sample preparation as well as the detection by high performance liquid chromatography, capillary gas chromatography coupled to tandem mass spectrometers or high resolution mass spectrometry should enable the lowest possible detection limit by use of minimal biological sample volumes. To get a first hint of a possible background level, the analytical methods were applied to urine samples of about 40 persons for each chemical. For Di(2-propylheptyl)phthalate and 2-Mercaptobenzothiazole first results are presented from population biomonitoring.

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1. Introduction

The German Human Biomonitoring (HBM) Initiative is a collaboration venture between the German Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety (BMUB), the German Federal Environment Agency (UBA) and the German Chemical Industry Association (VCI). The aim of the project is the development and application of biomonitoring methods for selected chemical substances for which no suitable analytical procedures exist by now. Within this project, the VCI has taken the responsibility for method development, while the BMUB, together with the UBA, takes care of the application in population studies. Up to 50 new methods will be developed between 2010 and 2020. A high-ranking panel of biomonitoring experts from academia, industry and relevant public authorities supports and advises the cooperation partners in their efforts.

The first step in the HBM project is the selection of an appropriate and suitable chemical substance according to the following criteria: (1) the substance might be taken up by the population in detectable amounts, (2) the substance should be of particular relevance to human health, and (3) no biomonitoring method exists at the moment which allows a specific and sensitive detection of environmental exposure.

Examples for such substances are plasticizers, foam components, flame retardants, antioxidants and UV filters. Since 2010, altogether 34 substances have been jointly selected for method development by VCI and BMUB (UBA-Website, 2016a,b; Kolossa et al., 2016). Another sixteen substances will be identified, discussed and selected until 2020.

After selecting a candidate substance for the HBM project which meets the criteria mentioned above, the development of the analytical method commences. As a first step, an appropriate biomarker needs to be identified. Relevant information about the biomarkers' metabolic properties may be gained from either animal or human kinetic studies, or be based on experience with the metabolism of chemically similar substances and expert judgement. The marker needs to be specific for the chemical of interest, but it is not necessary that it represents its main metabolite. Urine is the preferred matrix as it involves non-invasive sampling. With respect to analytical requirements, i.e. the typically very low concentration levels in biological specimens collected from the general population, high performance liquid chromatography (HPLC) or capillary gas chromatography (GC) coupled to tandem mass spectrometers (MS/MS) or high resolution mass spectrometers (HRMS) are employed. As sample volumes are usually critical when multiple parameters need to be analyzed from population surveys, the methods are optimized for low sample volumes (1 mL and less). On account of the usually low biomarker concentrations, limits of quantification (LOQ) need to be as low as possible. In a final step after the validation of the method according to generally accepted criteria (DFG, 2012), the method is applied to the analysis of urine samples derived from about 40 randomly chosen volunteers who are not occupationally exposed to the substance of interest. This pilot study should confirm both the validity of the method and the adequacy of the biomarker; it also provides a first estimate of the background exposure.

Part of the method validation is the cross-examination by a second laboratory from members of the scientific working group "Analyses in Biological Materials" of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the German Research Foundation (DFG). It is noteworthy that the examination comprises a full practical test and check of the validation criteria specified by the authors. The method including the examination results is published online by the DFG in open access. A publication of the method by the authors in a peer-reviewed international journal is also part of the project aims and agreement.

Fourteen new biomonitoring methods have been developed successfully up to now, among them the substances di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH), di(2-propylheptyl)-phthalate (DPHP), 4,4′-methylene diphenyl diisocyanate (MDI), Hexabromocyclododecane (HBCDD), 4-nonylphenol (NP), 4-*tert*-octylphenol (OP), *N*-methyl-2-pyrrolidone (NMP), *N*-ethyl-2-pyrrolidone (NEP), 2-mercaptobenzothiazole (2-MBT), 3-(4-methylbenzylidene)camphor (4-MBC), 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT), di(2-ethylhexyl)terephthalate (DEHTP), Lysmeral and 5-chloro-2-methylisothiazolinone/methylisothiazolinone (C(M)IT/MIT (3:1)). Some of these methods have also been fully published according to the project agreement mentioned before (Kolossa et al., 2016; UBA-Website, 2016a,b).

As it is important not only to measure a body burden but also to evaluate the concentration level from a toxicological point of view, the German Human Biomonitoring Commission (HBM Commission) at the Federal Environment Agency (UBA) derives toxicologically i.e. health based Human Biomonitoring–values (HBM-values) which help to interpret the relevance of the exposure levels observed. The HBM Commission consists of independent scientists and experts from authorities, appointed by the President of the German Environment Agency. Up to now for seven substances (Hexamoll™DINCH™, DPHP, NMP, NEP, HBCDD, 2-MBT, 4-MBC) HBM values have been derived. HBM values are regularly updated on the website of the HBM-Commission (UBA-Website, 2016a,b; Kolossa et al., 2016).

The new developed methods are subsequently applied e.g. in the framework of the German Environmental Surveys (GerES) or to samples of the German Environmental Specimen Bank (ESB) – both governmental programs under the jurisdiction of UBA.

For the whole project – starting from the selection of a chemical and supervising the development of the analytical method up to providing toxicological input for an independent derivation of health based values – an intensive collaboration between governmental agencies and chemical industry is required. For this reason, a VCI project group was established to identify appropriate and

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